THE PATHOGENESIS AND PATHOLOGICAL ANATOMY OF ENLARGED PROSTATE.

FROM THE PATHOLOGICAL LABORATORY OF THE BOSTON CITY HOSPITAL.

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THIS work is undertaken largely with the view to investigate the conclusions of the monumental work of Ciechanowski.[1, 2] To him, more than to any other, are due the thanks of the profession for new and careful work and for deliberate and conservative conclusions.

For personal direction and help in this study I wish to give the most sincere thanks to Dr. F. B. Mallory. The surgical specimens have been very kindly given to me by Dr. Paul Thorndike, and for unlimited access to post-mortem material I am indebted to Dr. Councilman and Dr. Mallory.

The number of senile prostates examined was thirty-seven, of which twelve were enlarged, twenty-four normal in size, and one small.

Urinary symptoms, which at present may be loosely designated "prostatism," are seen in many men over fifty. The proportionate number may not be determined with any accuracy. Thompson held that there might be a slight enlargement of the prostate without symptoms in about one in three men over sixty years, and that a marked enlargement is seen in one in seven after that age. The symptoms are increased frequency of micturition, incomplete emptying of the bladder, with residual urine, or distention with dribbling. Of men with these symptoms, it is estimated that only 15 per cent. have enlarged prostate; and, although it will be shown that disease and change in the bladder-wall are probably important factors in producing this condition of prostatism, nevertheless, they alone are probably not sufficient, for one never sees senile vesical inertia with retention in women, where directness and permeability of the urethra are not affected. Hence, mechanical obstruction in the form of prostatic enlargement at the outlet of the bladder must be always important among the elements of "prostatism."

I have attempted in the following notes to compare and record differences in senile prostates, enlarged, normal, or small, and in some degree to study the accompanying bladder-wall changes.

Methods.—In general, for histology, preservation in Zenker's fluid was found the best. Formalin, 10 per cent. solution, was used for hardening and preserving specimens for gross examination, and also for special nerve-stains. The prostates were embedded, some in paraffin, many in celloidin, and cut of varying thicknesses (seven to twelve microns). All stains were used, but principally Mayer's hemalum and eosin, Van Gieson's stain diluted and with enough additional picric acid to make the yellow predominate over the red. For minute changes in the proportions between muscle and connective tissue, Mallory's connective-tissue stain [50] gives marvellous detail. Nerves and nerve-sheaths were stained by Pal's modification of Weigert's method.[51] For elastic tissue, Weigert's stain [52] was used.

PART I.

THE BLADDER-WALL IN VESICAL INSUFFICIENCY.

Examination in the gross of a bladder and prostate cut in a sagittal plane, through the urethra, in subjects over forty-five years, shows in over half the cases, at the origin of the urethra, a distinct lip, rising slightly above the level of the urethral floor, then dropping sharply in a perpendicular behind, to form the anterior wall of a bladder-pouch (Fig. 1). This lip is formed by the prostate, which may or may not be enlarged, and the pouch varies much in size, not corresponding necessarily to the size of the prostate. This pouch contains the

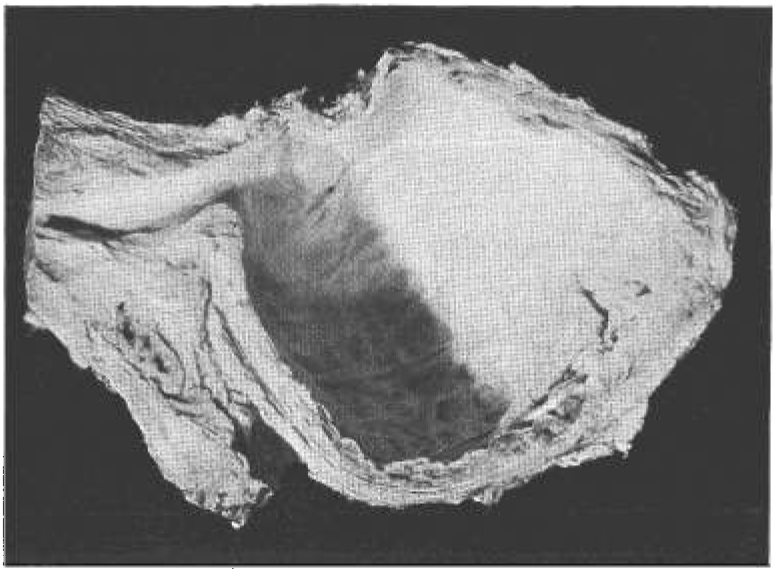

Fig. 1.—Sagittal section of senile bladder and prostate, showing the fibrous bands in the wall of the atrophic bladder, the retroprostatic pouch, and the orificial prostatic lip.

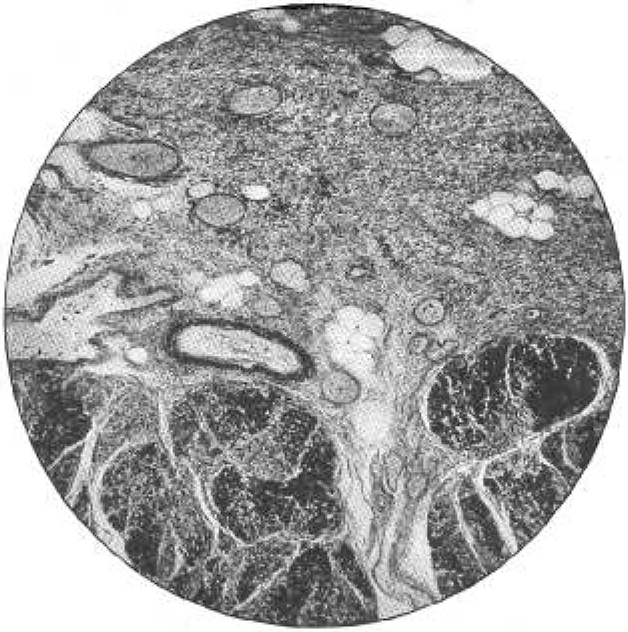

Fig. 2.—Showing fibrous infiltration of the bladder-wall muscles.

residual urine and is a prominent factor in prostatism, and, inasmuch as it is found without enlarged prostate, we must seek a partial cause of it, at least, outside the prostate.

What changes in the bladder-wall are to be seen where this pouch and vesical insufficiency exist?

At least five possible changes are to be considered:

I. *The Presence of Fat in the Senile Bladder.*—Dittel [17] laid the cause of senile bladder to fatty degeneration. Maas [47] laid it to fatty degeneration of hypertrophic bladder-muscles. Rokitansky [68] describes it loosely as a colloid degeneration. Ciechanowski [1, p. 207,] found fat between the outer muscle-bundles in streaks, occasionally subserous, more rarely submucous, where it is never normal; and he concludes that bladder insufficiency does not depend on fatty degeneration, because this fat is not seen by any means in all cases and only rarely in muscle-cells.

I have seen it between muscle-bundles and subserous, where the fat globules are large and borne in cells with relatively little protoplasm; that is to say, having the characters of normal adipose tissue. Only occasionally muscle-cells show fine fat globules, and then only in bundles where other and much more extensive and important changes, as will be noted, are present. With this slight exception, fat in the bladder-walls apparently has only the significance of fat deposit anywhere.

II. *The Presence of New Connective Tissue and of Muscle Changes in the Senile Bladder.*—Orth [61] has noticed atrophy of bladder-muscles in chronic dilatation of the bladder. Launois [43] holds that by overwork the muscle elements become surrounded with fibrous tissue, which finally suppresses their action. Guyon [32] believes that all changes of a connective-tissue kind are due to the impaired nourishment consequent on arteriosclerosis of the bladder. Bohdanovicz, quoted by Ciechanowski [1, p. 207,] holds also that over-exertion of bladder-muscle leads to fibrous changes; but he ignores cases of bladder insufficiency where no signs of previous hypertrophy are to be found; cases, in other words, where no cause for bladder-muscle hypertrophy exists. He gives no heed also to chronic inflammation as a possible cause of some of the changes which he observes. In the study of senile changes in the bladder-wall, therefore, such changes as are plainly due to chronic inflammation should be clearly distinguished.

Ciechanowski has done so, and, shutting out those cases which have the submucous fibrous deposit of old cystitis, makes a series of careful measurements of transverse sections of bladder-wall. He adds together the total area of muscle-elements and compares it with the area of the interstitial connective tissue in section of definite size, submucous and subserous tissue being excluded. He finds that the amount of connective tissue compared to that of muscle in the highest grades of arteriosclerosis varies between 1 : 4 and 1 : 1.2. The fraction for the normal bladder given by both Orth and Ciechanowski is 1 : 3. The latter then observes that interfibrillary and interfascicular fibrous tissue only appears increased when there is a considerable amount of new connective tissue about the vessels. Hence, shutting out these cases, which from the apparent vascular origin of the fibrous tissue seem to be inflammatory in origin, he concludes that the connective-tissue increase is only apparent and fills in the place of truly atrophied muscle. He compares cases which differ only in respect to age with no cystitis, cases where no cause for bladder-muscle hypertrophy exists, and finds his relation of connective tissue to muscle go from 1 : 3.5 up to 1 : 2, according to age alone, and hence concludes that the change is true senile atrophy. Into this matter I have not gone with detail. My specimens (Fig. 2), excluding those apparently inflammatory, show irregular distribution of the new-formed fibrous tissue within the muscle-bundles. Such fasciculæ of muscle as remain stain well and show striæ. The fibrous tissue between the separate muscle-fibres, stained by Mallory's connective-tissue stain, is repeatedly seen in amounts greater than in the bladder-wall of youth. I am inclined, therefore, to believe that, although the senile bladder having no obstruction may undergo atrophy to a degree similar to that of the whole muscular system, at the same time there is apparently a tendency to a true bladder sclerosis, an irregular growth of new connective tissue within muscle-bundles, and at the expense of the fibres. This could be explained on the ground of probability as being a sequela of chronic inflammation, but that repeated sections show this quantitative change without submucous or subserous fibrous thickening or any remains of round-cell infiltration.

III. *The Presence of Sclerosis in the Vessels and Walls of the Senile Bladder.*—Much complicated and ingenious theorizing has been devised to demonstrate a sequent connection between such a sclerosis and the conditions found in prostatism. For example, a senile change of both bladder and prostate; more specifically, changes in structure in the parts in question which depend upon a general arteriosclerosis with modified blood-supply,—that is, that prostatism depends upon the local effects of a remote or general cause. A modified form of this theory declares that prostatism is a result of sclerosis of the vessels of the urogenital system only.

Another subdivision under this theory makes the process a local one, consisting in so-called " sclerosis" of bladder and parts connected, that is, an increase of connective tissue in the bladder-wall, at the expense of the muscle, with contraction in places, lack of tone and distention in other parts, such as the formation of a pouch behind the prostate and the constant pressure of residual urine and its consequences.

I find that cases with intima and media thickened and lumen correspondingly small show the fibrous change in the muscles. On the other hand, cases with little or no change of vessels within the bladder-wall may show a considerable loss of muscle-fibres and corresponding new interfibrillary or interfascicular connective tissue.

It seems apparent, then, that there occurs in many senile bladders a quantitative change in the structure of the walls not due to inflammation, and that this change, while it may correspond remotely to the general muscle changes of old age, does not depend on arteriosclerosis within the bladder-wall.

IV. *As to the Rôle of Urethral Obstruction in the Senile Bladder.*—In the development of prostatism and of the vesical pouch we have seen that the first element, and the one which may alone be sufficient, is atrophy of the bladder-muscle and replacement of the muscle by fibrous tissue. Such a bladder is less elastic than the unimpaired bladder; it tends more frequently to empty itself, and contracture, the usual rôle of new connective tissue, takes place. Grossly, fibrous bands intersect and form sharp, submucous ridges (Fig. 1). This more or less inelastic sac now no longer tends to maintain its natural ovoid form, and, weighted with urine by force of posture and gravity, it falls towards the rectum and perineum. The orifice of the bladder, however, the beginning of the prostatic urethra, situated above the isthmus of the prostate at the apex of the trigonum, is fixed. The prostate is held firmly in relation to the pubes by the puboprostatic or anterior ligaments of the bladder. At this point, slightly posterior to the isthmus, in the plane of the posterior urethral sphincter, there forms an orificial lip, behind which falls away the pouch. To form this lip there need be no prostatic enlargement; in fact, the total volume of the prostate may be diminished. On section sagitally (Fig. 3) this lip is covered with mucosa, and immediately beneath it, and extending forward to be continuous with the prostate, is always a collection of prostatic glands. They may be few in number, at times dilated, but always present. Beneath them and cut transversely is the more or less wedge-shaped section of the inferior part of the posterior sphincter (Fig. 3, *s*). From this condition, all stages up to the development of a true middle lobe may be seen. And this form of enlargement, like other forms of clinically enlarged prostate, is essentially glandular. Ciechanowski has shown successive stages of the development of a nodular middle lobe in this situation by dilatation of this small group of glands (Fig. 3, *g*) just within the posterior half of the sphincter, and by increase of their surrounding tissue, extending downward and pressing always on the sphincter till the latter is fully and permanently dilated, is atrophied, and finally, under this middle lobe, dis-

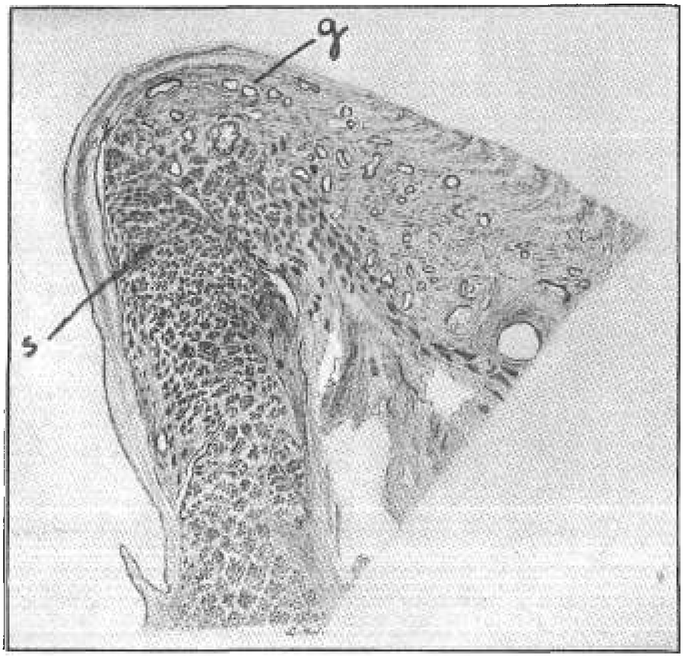

FIG. 3.—Showing the posterior orificial lip. At the left, forming the anterior wall of the retroprostatic pouch, is the wedge-shaped section of sphincter (*s*). Superiorly, just under the urethral mucosa, are the few isolated prostatic glands (*g*), which are always present, which serve as origin of the third lobe.

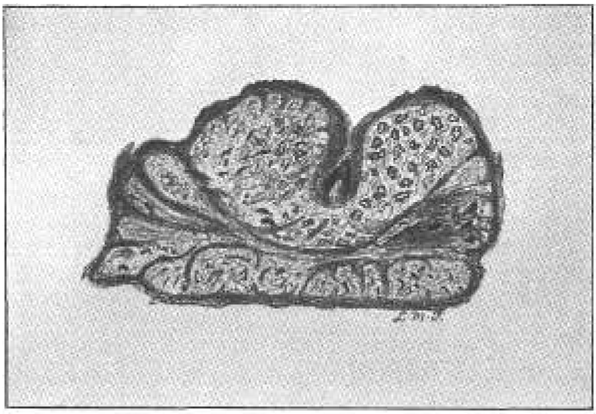

FIG. 4.—Showing a fairly distinct horizontal transverse fibrous partition in a coronal section.

appears. This prevents effective shutting off, and the prostatic urethra is likely to remain filled with urine and constant desire to micturate be present.

This nodular form of prostatic outgrowth may appear laterally, and so deviate or distort the urethra. If there is a real obstruction to outflow and not mere deviation of the urethra, and there be any reactionary power in the bladder-wall, its muscles will hypertrophy. Age and inflammation (*vide* V., *infra*) will limit or destroy this power of hypertrophy. And furthermore, hypertrophy of bladder-muscles already existing may yield rapidly before foul and persistent cystitis. Cases which show merely the posterior orificial lip and pouch behind, without nodular or valve-like urethral obstruction, never show bladder hypertrophy.

V. *On the Rôle of Chronic Inflammation in the Senile Bladder.*—Chronic cystitis is an important secondary cause of vesical insufficiency. The usual remote origin of the cystitis is a persistent and sometimes latent gonorrhœal infection; a continual aggravating cause is catheterism. As has been already stated, there is no evidence, gross or microscopic, that such inflammation is an essential in the changes observed in insufficient bladders. The bladder-wall in cases of long-standing cystitis may show the greatest degree of thickening. This thickening on section is made up partly of a round-cell infiltration of mucosa and submucosa, but mostly of a considerable submucous development of fibrous tissue, which in old cases raises all over the inner aspect of the bladder (Fig. 1) a tangle of crossing ridges. These ridges may be so prominent as to convert the inner aspect of the bladder into a succession of pockets or saccules. There is some new connective tissue formed between the bundles of muscles, with round cells here and there through it which show its inflammatory origin. New subserous fibrous tissue may less commonly form part of this thick wall.

The importance of chronic inflammation in the senile bladder lies principally in the fact that it rapidly intensifies all the changes and symptoms already existing. The bladder suffering from it is less tolerant, contracture is greater, atrophy is more rapid.

VI. *On the Presence of Stone in the Senile Bladder.*—This is of great frequency, but often undemonstrated before operation because (*a*) the symptoms of stone are masked by those of obstruction and cystitis; (*b*) the calculus forms and remains in the retroprostatic pouch, and may be even quite enclosed in one of the saccules referred to. Large stones felt by rectum sometimes are mistaken for enlarged prostate.

Conclusions.—(*a*) Senile vesical insufficiency, which may be called clinically "prostatism," is not a single entity, but a complex condition. It has a distinct anatomical basis and may be due to one or more of several causes. (*b*) It is not due to fatty degeneration or infiltration of bladder-muscle. (*c*) It is not due to arteriosclerosis of bladder-vessels. Changes in walls of blood-vessels have no constant relation to change in the bladder-wall. (*d*) The causes of bladder insufficiency are:

(1) Atrophy of bladder-muscle and new growth of connective tissue, finally infiltrating the muscles.

(2) Mechanical obstruction at the beginning of the urethra. This may be simply a posterior lip at the orifice in front of a retroprostatic pouch; it may be a true middle lobe of the prostate acting as a valve; it may be a nodule or enlargement of one or both lateral lobes protruding into the urethra.

(3) Chronic cystitis intensifies these two causes, namely, muscle atrophy and obstruction at the exit, by means of the structural changes due to inflammation.

(4) Stone in the bladder increases the symptoms, but is probably rarely a primary cause of insufficiency.

(*e*) Although structural changes in the bladder-wall may alone be sufficient to cause prostatism, the most important factor is probably obstruction. (*f*) The tendency to all these changes increases with age; and, finally, (*g*) the most marked cases are those where atrophy of bladder-muscles, connective-tissue infiltration, enlarged prostate, and chronic inflammation are all present.

PART II.

ON THE STRUCTURE, GROSS AND FINE, OF ENLARGED PROSTATE.

A. *The Normal Prostate.*—The normal prostate is classically and well described as a chestnut-shaped body adjoining the neck of the bladder, inclosing the first part of the urethra. The urethra runs nearer the anterior than the posterior aspect of the gland, that is, about .7 centimetre from the former and .9 centimetre from the latter, but it varies.[25] The narrow end or apex of the prostate is directed downward and forward to within 1.5 centimetres of the symphysis, to which it is connected by thickenings of pelvic fascia. The posterior part or base is close to the rectum, through which it may be felt, about six centimetres above the anus.[48] Its measurements are about 3.5 centimetres across at its widest, *i.e.,* bilaterally; three centimetres from base to apex, and about 2.5 centimetres in thickness, *i.e.,* in the direction of the urethra. The weight of the normal prostate ranges from 13.6 grammes to 21.4 grammes, the average being eighteen grammes.[72] These limits are not strict. A sheath derived from the rectovesical fascia incloses the prostate and contains the prostatic veins. This capsule is fairly distinct. The rectal surface shows two grooves which meet in front and indicate the course of the seminal ducts. The gland presents a lateral lobe on each side of the base, and a middle portion or isthmus which is included between the ejaculatory ducts and the neck of the bladder.

The prostatic urethra, about three centimetres long, is dilated in its middle, where there arises from its floor the verumontanum (Colliculus seminalis, Caput gallinaceum).[69] The ejaculatory seminal ducts, passing forward from the seminal vesicles, traverse the lower part of the prostate and empty into the urethra by two slit-like openings on or very near the crest of the caput. The prostatic ducts empty through the wall of this portion of the urethra by twelve to twenty (fifteen to thirty-two, Svetlin, quoted by [75]) openings, most of them on the floor of the urethra in a fossa on each side of the caput, called the prostatic sinus. The two largest prostatic ducts empty at the caput just behind the mouths of the ejaculatory ducts (Walker, loc. cit., 253). In the middle line, close in front of the orifices of the ejaculatory ducts, in the forward part of the caput is the prostatic utricle (Sinus pocularis, Uterus masculinus). This is a blind pocket, about .8 centimetre long, extending upward and backward beneath the isthmus.

Histologically speaking, the prostate normally is made up of smooth muscle-fibres, of rather cellular connective tissue, and of true gland-tissue in the proportions roughly of 1 : 1 : 2, together with more or less elastic tissue. On examination of a section here and there, no idea of a definite order of arrangement of these elements may be obtained. Walker (loc. cit., 244), by a most careful study of serial sections in the dog, has come to the following conclusions with regard to the distribution of

Muscle in the Prostate.—" That the vesical end of the prostate is surrounded by a thick muscle composed of longitudinal, circular, and oblique fibres, from which a large process projects anteriorly and posteriorly between the two glandular hemispheres; and a thick sheath is sent out on either side, which encases the fore, lateral, and dorsal surfaces. The posterior process extends to the urethral end, where it spreads out round the external surface in that region. From these muscular divisions, septa pass into the gland and surround the lobes in a circular and longitudinal manner, giving to each lobule two distinct coats. The muscle-coats of the urethra and bladder are inserted into the prostate and not continued through it, and the urethral coats in the prostatic portion are replaced to a considerable degree by prostatic substance." Striated muscle in the prostate is found only as a part of the external sphincter of the bladder at the urethral end of the gland, principally as a thick layer of circular fibres.

The Connective Tissue part of the stroma can be only fully recognized and duly appreciated when stained by Mallory's connective-tissue stain. It may then be seen to form one-fourth or less of the gland, a fairly dense, fibrous structure, rich in

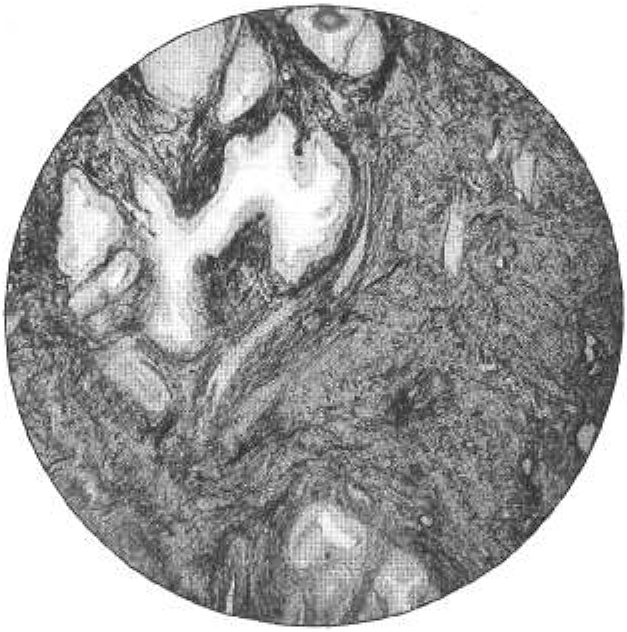

FIG. 5.—Showing the distribution of elastic fibres in the normal prostate.

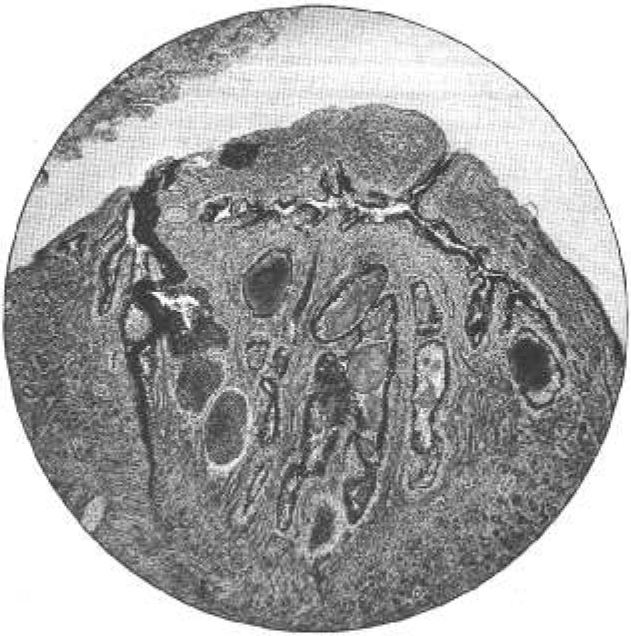

FIG. 6.—Showing the senile caput with its apical duct, amylaceous bodies, and a slight degree of small round-cell infiltration.

cells at birth and in youth, becoming more fibrous as age advances. On gross coronal section (Fig. 4) in the normal prostate of middle life and later, a distinct transverse, horizontal, fibrous partition is seen. This runs in a plane across the gland about one-third of the distance from the urethra to the posterior surface, and, as it approaches the sides, inclines downward towards the lateroposterior angles. Branches of this plane often curl upward to more or less encapsulate the lateral lobes, merging finally with the sheath.

Microscopically, these septa, more dense and fibrous than the rest of the connective-tissue stroma, send out in all directions ramifications of increasing fineness round and between the muscle-masses, between and supporting the gland lobules. This tissue accompanies the innumerable capillaries of the organ. Between these smallest vessels and the cellular stroma in dogs, Walker finds a membrana propria made of finest connective fibrillæ. Regnauld,[67] quoted by Walker, finds none; Langerhans cannot differentiate it; Walker cannot demonstrate it in the human. A few small round cells, plasma cells, and leucocytes are to be seen normally, but in the larger septa rather than near the lobules a point of difference to be noteworthy later.

Elastic Tissue in the normal gland has been carefully observed by Walker (loc. cit., 248), who also quotes Antonini.[5] Walker finds surrounding the urethra, just under the mucosa, a sheath of longitudinal fibres. The outer fibres spread into the gland and form a figure-of-eight net-work round each prostatic duct, apparently making an elastic sphincter for each. Extensions are seen into the larger fibrous septa, and from there fine fibres arrange themselves in a circular manner round the alveoli (Fig. 5). The caput is especially rich in elastic fibres. They are arranged round the utricle about each ejaculatory duct, besides a considerable submucous layer of it all over the prominence.

The *glandular portion* of the normal prostate consists of thirty to fifty simple tubes, straight in the embryo, later branched, and finally forming complex lobules. They unite into a smaller number of excretory ducts, and, finally, empty into the prostatic sinuses as already described. In the upper portion of the prostate the alveoli are smaller and more saccular, smallest at the exit. In the lower part of the gland the tubules are longer [71] (Quain, loc. cit.). In the anterior commissure the tubules are relatively few in number and simple.

The epithelium lining the glands in the dog have been described with the greatest exactness and detail by Walker, and in man by Langerhans.[42] The cells are arranged in one layer and vary in shape,—long, columnar, cuboidal, or even irregular, with relatively large nuclei near the base in the primary lobules, while in the ducts the cells are more flattened with nuclei near the centre, and at the exits are merely squamous, of the urethral type. The alveolar secretion is seen as a shrunken, finely granular mass, staining pink by eosin. An occasional desquamated granular epithelial cell is seen, and in senile prostates, which in no other way deviate from the normal, there are so frequently seen round, stratified, so-called *amylaceous bodies* that they must be mentioned in describing the normal prostate. They vary in size, up to filling of the saccule, and consist often of clearly defined concentric strata. Some stain red, others blue by Mallory's connective-tissue stain.

The *Caput gallinaceum* is made up of connective tissue and muscle, together with a relatively large amount of elastic tissue. The glands of it are near the summit and open by a common duct, just anterior to the centre of the crest (Fig. 6). Muscle surrounds these glands as elsewhere, but does not extend to near their orifices. Adenoid tissue, described by Walker (loc. cit., p. 250), I have not seen. He says, "In quite a number of prostates, bits of adenoid tissue were scattered here and there throughout the tissue, generally near the lateral surfaces. Two or three small nodes are usually near together with a rather thick layer of connective tissue between them. In some of the nodes are minute channels lined by endothelium; these are most probably lymph vessels."

The *vessels* of the prostate are branches of the vesical, hæmorrhoidal, and pubic arteries. They pass into the prostate along with the larger connective-tissue septa, where they break into smaller twigs, follow the ducts to the lobules, and break up into capillaries about the alveoli.[64] On the sides and base of the prostate in its fibrous sheath, the veins form a plexus. This is highly developed in old subjects. These veins behind pour into branches of the internal iliac. In front they empty into the dorsal vein of the penis.

Lymph channels and vessels may be found between the two layers of the fibrous sheath.

The *nerves* are derived from the hypogastric plexus of both sympathetic and central origin. They contain both medullated and non-medullated fibres, and show here and there ganglion cells. They are seen in the posterior and lateral surfaces and pass along the fibrous trabeculæ towards the alveoli. Their course is extremely difficult to follow, and practically nothing is known of their termination.

B. *The Senile Enlarged Prostate.*—The character of the changes which together may be seen to make up the structure, gross and fine, of the enlarged prostate, is to be most clearly understood by a separate presentation of the changes observed in each structure, particularly the glands, the muscle, and the connective tissue.

Gross.—The senile prostate which has suffered general enlargement attains a greater size than that in which one lobe has increased in size. The limits of *weight* of Thompson's cases were twenty-two to 180 grammes; of mine, twenty-seven to 180 grammes.

The capsule varies much in strength and thickness,—in some cases the gland may be easily shelled out, in others it is hard to differentiate gland from capsule.

The *consistence* of the enlarged gland may be extremely spongy, through degrees of increasing firmness, up to a hard, fibrous feel. The gross appearance of a *cut section* corresponds to these differences in feel, that is, from that of a fine sponge to that of a cross cut of a fibroid of the uterus. Some show on the cut surface many distinct, encapsulated, round, fibrous bodies, which protrude above the level, as if relieved from the compression of a tight capsule. This is the "Knotige" form of enlargement described by the Germans. From all, except the hardest, there comes, from a cut surface on squeezing, a slightly gelatinous turbid fluid.

The distribution of the enlargement is irregular. It appears most often in the lateral lobes, next often in the lateral lobes and in the form of a middle lobe, next often as a middle lobe alone, and, lastly, as one lateral lobe. The anterior commissure rarely suffers enlargement, a fact of considerable significance, as will be shown.

It is now necessary briefly to consider the gross details and immediate mechanical effects of enlargement of the prostate in each of the varieties just mentioned.

1. *Bilateral Enlargement.*—In this form the urethra is increased in length, and its cross section is transformed from a triangle to a vertical slit. To do this, the side-lobes have grown downward and backward, and the floor of the prostatic urethra is depressed below the level of the posterior lip of the bladder orifice. In this manner the posterior obstructive lip (Mercier's bar) can form even when the hypertrophy is of the lateral lobes; the sphincter remains normal, while the urethral floor anterior to it is depressed, and a bar is formed without the necessity of bringing in an hypertrophied sphincter to explain it. It is in this way, together with the bladder-wall changes, that retention begins in cases of side-lobe enlargement.

2. *The Formation of a Middle Lobe.*—This takes place either as a part of a general enlargement or alone. Its interest grossly is in its relation to the posterior half of the sphincter muscle at the orifice. The older observers[16] held that the middle lobe arises from the portio intermedia, anterior to the sphincter, and grows up between the urethral mucosa and the posterior half of the sphincter. The sphincter thus comes to lie always behind a sort of valve-like tumor, later becomes flattened out, and finally disappears through atrophy. More careful later observation[40] makes it probable that this polypoid middle lobe has nothing to do with the posterior commissure

or isthmus, which is always below the sphincter, but that it develops from the few isolated, prostatic acini which lie between the mucosa and the sphincter at the orificial lip of the bladder (Fig. 3, *g*'). All agree that the sphincter posteriorly disappears, either being pressed upon by the new growth above it, or suffering infiltration by the growth. This middle lobe may act as a cause, therefore, of either retention or incontinence; retention, if the growth fit like a ball-valve exactly into the orifice, incontinence, if it does not fit the orifice, and at the same time does continuously stretch and so destroy the tonus of the sphincter. If, besides the pressure from above, from the middle lobe, there is also pressure from below and in front from enlargement of the rest of the prostate, the sphincter becomes pushed up into the true bladder-wall. Thus, so far as function goes, the sphincter disappears, because in this position it has no relation to the orifice, and the bladder must be then continuously incontinent unless there be a valve. At this point, however, it must be made finally clear that these ball-valve growths which arise from the relatively isolated prostatic glands under the mucosa of the orifice, are to be distinguished from the point of view of mechanics, from the posterior lip already described. This *barriere vésicale* of Mercier is a mechanical obstacle; it favors the formation of a pouch, but its pathogenesis is that of the third lobe. They both arise from dilatation of prostatic glands,—those of the valve-like lobe coming directly from the isthmus and tending to fill the exit, while the posterior lip obstruction is somewhat behind the orifice. It is definitely clear that this bar is never due to hypertrophied sphincter.

3. *Enlargement of One Side-Lobe.*—This is relatively uncommon. It develops in the direction of least resistance, which seems at first to be towards the periphery, but finally is always towards the urethra, where it narrows that passage, lengthens it, and causes it to deviate laterally, according to the contour of the new growth. Unless it be sufficient in amount actually to interfere with the patency of the urethra, there is

likely to be little retention or incontinence, unless there be also some of the other causes present in sphincter or bladder-wall.

4. *General Enlargement.*—This is one of the common forms where, besides bilateral enlargement, there is also developed a third lobe. The bladder-pouch appears early, and the urethra suffers narrowing from side-pressure, or is obstructed, or is held patent according to the final relation in size between the enlarged portions of the prostate in a given case. In short, the changes in function due to general enlargement are a combination of the changes seen in enlargement of the separate parts.

Microscopic.—It now remains to go into a detailed microscopical study of the enlarged prostate.

Proportion of Constituents.—In the normal prostate, as we have seen, the proportion of muscle, connective tissue, and gland tissue is roughly 1 : 1 : 2. In the enlarged prostate, in practically all cases, the observer is at once impressed with the relative increase in the area taken up by glands; no definite proportion, however, can be worked out.[55]

Muscle in Enlarged Prostate.—The muscle-sheaths which start at the vesical end remain about fixed in size, but often show some fibrous infiltration. The coats which surround the acini and ducts no longer show a clear division into two coats; in fact, more often around dilated glands only indistinct traces of muscle tissue remain. Remains of the larger septa, from which the coats that surround the glands arise, may be seen cross-cut here and there in nearly all sections. The cells stain well, the nuclei show no active subdivision, and a close intermixture of fibrous tissue with each bundle exists. Many groups of elongated spindle-shaped cells, which I believe hitherto to have been considered new, smooth muscle cells, stain blue by Mallory's connective-tissue stain, and they should without any doubt, therefore, be classed as new connective tissue. About some glands may be seen portions of muscular capsules occasionally thicker than those in the normal gland. This is the only suggestion of true "hypertrophy" to be seen in enlarged prostate.

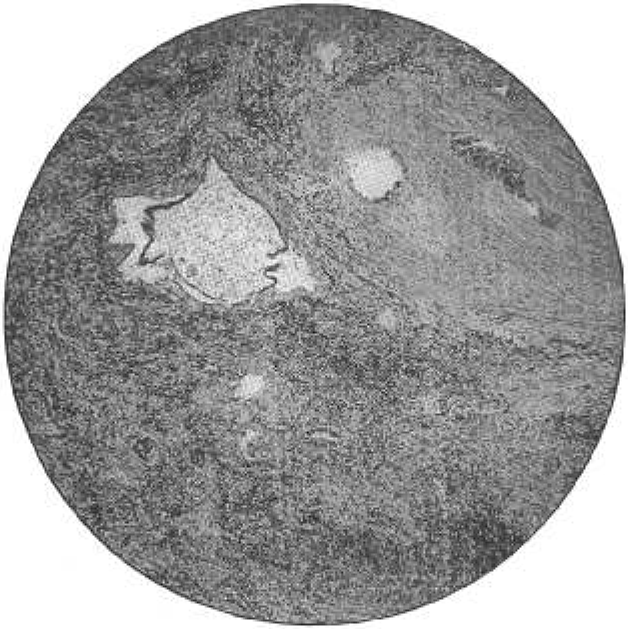

Fig. 7.—Showing areas of scar-tissue, round-cell infiltration, and glands wholly or partly denuded of epithelium.

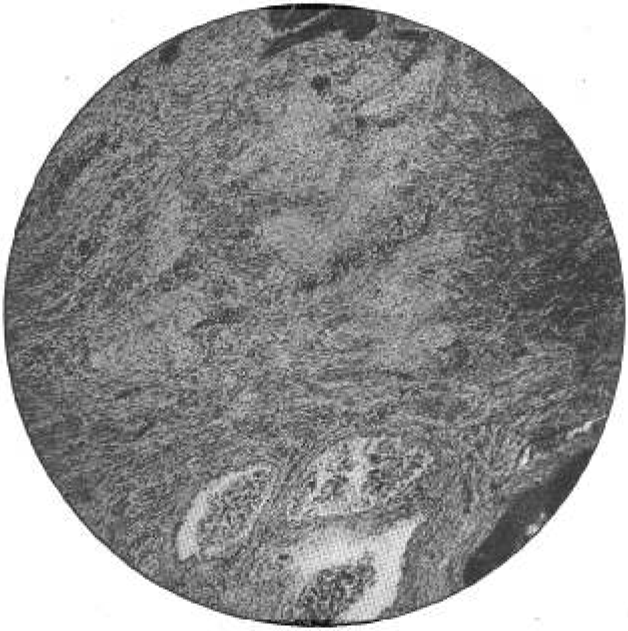

Fig. 8.—Showing well-marked scar-tissue areas and denuded glands with pathological contents.

The *connective tissue* part of the stroma may be greatly increased in relative quantity. The average amount could be roughly estimated as two or more times as great as that of muscle. It is richly cellular for the most part, but presents two differences from that of the normal prostate. The first of these differences, the real importance of which was first made clear by Ciechanowski, is the presence of small round cells (Fig. 7). These cells are seen most often in the fibrous tissue near the acini; they may be diffusely distributed (Fig. 16), and isolated groups of them are also seen. Such groups may, of course, be in relation to glands not cut by the section. The groups are entirely irregular in outline and present no suggestion, in the way of minute channels or pellicle, of the lymph nodes of Walker. The nuclei are single, relatively large, stain deeply with basic stains, and the cells cannot be distinguished from lymphocytes. They are similar in kind and distribution to those seen in chronic mastitis. Examination of every large prostate shows these cells. Many cases show undoubted polynuclear, round cells.

The second distinguishing feature of the new fibrous tissue is the presence in it, here and there, of irregular masses of nearly hyaline, nearly homogeneous, dense, poorly staining fibres, in short, masses of scar-tissue (Figs. 7 and 8). About such scars small round cells may be seen. The masses may be in relation to tubules or apparently apart from them. In the midst of such masses of scar-tissue may nearly always be found remains of glands (Fig. 8). Such gland-remains are usually denuded of epithelium or collapsed by pressure, or, in cases, the presence of a so-called amylaceous body may alone show the previous presence of a gland. Within the scar-tissue may also be seen clumps of the spindle cells of new connective tissue or small areas of round cells.

Such associated appearances, namely, small round cells, well staining spindle cells, and scar-tissue, can be looked upon probably as stages of one inflammatory process.

The relation of these stroma changes to the glands is the next question of importance. In general, all the changes named are seen to a far greater extent near the central or urethral part of the prostate than near the periphery. The round-cell clumps in particular are seen repeatedly near the walls of the larger terminal ducts (Fig. 9). In addition, there are often areas infiltrated with polynuclear leucocytes. These areas are of any size, even up to small abscesses visible to the naked eye (Fig. 10). Fairly definite rings of the new connective-tissue cells are seen in places near ducts, and the scar-tissue, as has already been noted, may be found many times quite inclosing and compressing a duct of moderate or large caliber, some of these even to complete obliteration. These evidences of proliferation in the stroma are seen, as a rule, not between or round the glands which have suffered dilatation. This is a point of great importance, as will be seen in considering the changes in the glands in an enlarged prostate.

Elastic Tissue in the Enlarged Prostate shows little or no change in quantity,[53] but stains less sharply near dilated glands or near those which have purulent contents. The elastic fibres (Fig. 11) are less wavy and are more closely compact in bundles, as if pressed upon laterally by the dilated glands on one side and the stroma on the other. They form, therefore, in the enlarged prostate, narrow, dark bundles following the outline of the enlarged acini.

The Glands or Acini in Enlarged Prostate.—As has been said, the first impression on examining sections of most enlarged prostates is the apparent relative increase in the area covered by glands. The ducts are in many places wider and the glands are much dilated (Fig. 13). Two glands close together dilate till they are separated only by their respective linings of epithelium, and one or two degenerated supporting connective-tissue fibres between them (Fig. 12) ready to give way. In others, a shelf of fibrous tissue protruding into a lumen is the only remains of a previously existing partition. Other parts of these acini show changes due to dilatation also. The *epithelium* lining the glands and ducts of the enlarged prostate presents always marked changes. The cells are smaller, they are flattened, their nuclei stain less deeply, the

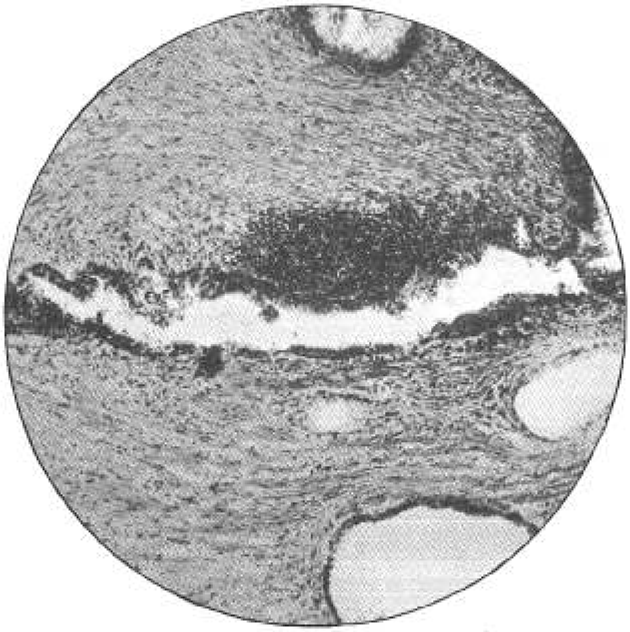

Fig. 9.—Showing round-cell infiltration with minute abscess formation in the wall of a prostatic duct. Dilated and denuded glands near by.

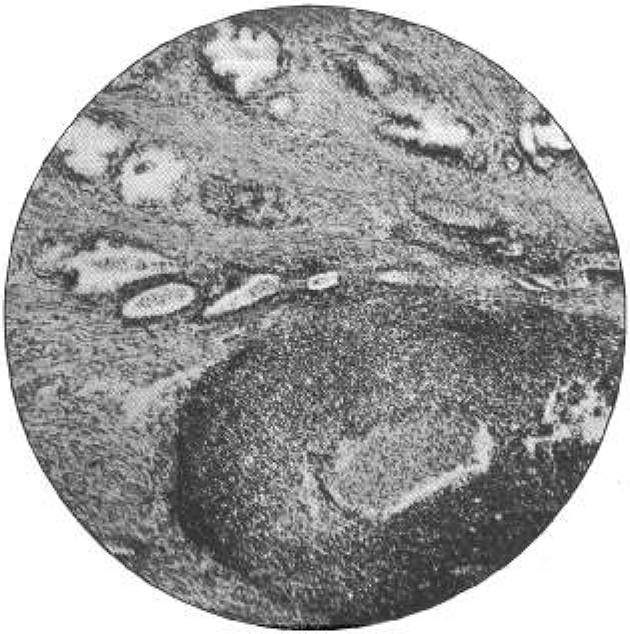

Fig. 10.—Showing microscopic abscess formation surrounding and including a prostatic gland.

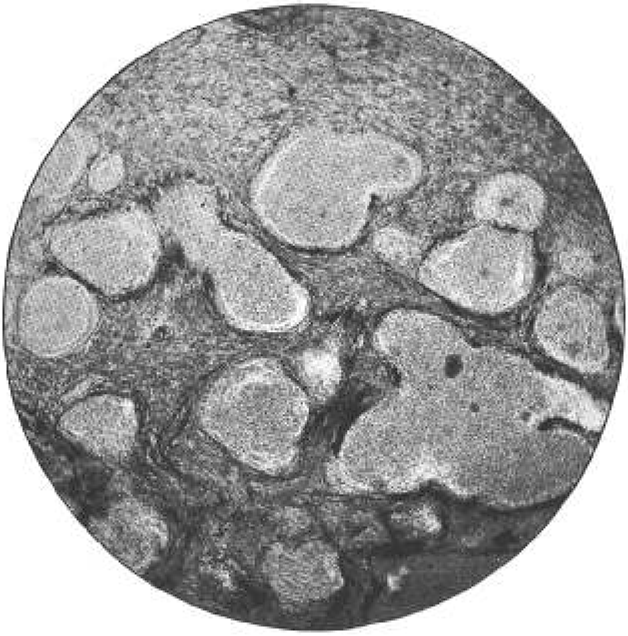

Fig. 11.—Showing bundles of elastic tissue squeezed between the dilated glands of enlarged prostate.

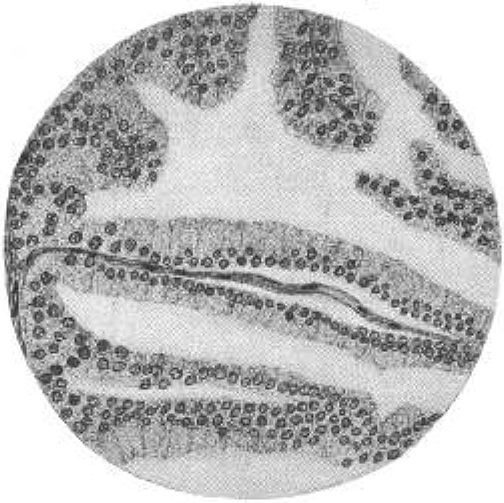

Fig. 12.—Showing a stage in gland dilatation; remains of gland-partitions in the form of shelf-like projections. In one place a single compressed line of connective tissue supports epithelium on each side of it.

cytoplasm becomes granular and stains faintly. In places (Figs. 7, 12, 13, 14) the cells have flattened until they are scale-like; in places they have desquamated. In some glands a series of six or more cells still connected together in a row may be seen lying free in the space near the place in the wall from which they have been separated. In other glands, a few flattened nuclei in the wall are the sole remains of the lining membrane, while the final stage of these changes shows no epithelium remaining, but only the gland contents lying free in a space in the stroma. In some of the acini, the degenerated lining-cells desquamate and coalesce in an ill-defined, poorly-staining, granular, or even amorphous mass in the centre of the dilated space, or in other glands, whether or not the wall has been denuded of epithelium, there are seen the so-called "amyloid bodies" or concretions. These are more or less stratified rounded bodies, staining red or blue by Mallory's connective-tissue stain, and contain within themselves small, granular bits of chromatin, often enough to suggest their origin in old epithelial cells. These bodies are constantly found in dilated glands of enlarged and normal-sized prostates, so often indeed as to warrant the belief that they are really a normal senile condition.

The granular or amorphous mass in the dilated gland-space may also show small, round mono- or polynuclear cells (leucocytes) in varying numbers, even up to an amount to make the glandular contents truly purulent. This is particularly seen in the larger spaces. The larger gland-spaces always have pathological contents, that is, epithelial products together with few or many leucocytes; they are never empty. The size of these dilated glands varies much, from the slightly distended tubule up to a macroscopic cyst or abscess. The form of the glands remains normal with some distention, but as the internal pressure increases they become quite round on section in every plane.

It is apparent, therefore, that the view held by Socin[70] and Ciechanowski is amply supported. In enlarged prostate, the essential change is a passive dilatation of the prostatic glands and ducts induced by the gradual accumulation in them of retained secretion, degenerated cast-off epithelium, and leucocytes. The process is probably not a physiological one because the greater the degree of dilatation the gland has suffered, the greater, as a rule, the number of leucocytes in it. The amount of cast-off epithelium in the gland-spaces suggests an increased activity of production of epithelium, it is true, but not neoplasmic in character. The lining membrane in their sections is only one cell thick, and the proliferation arises from cells which do not show the staining reactions of vigorous epithelium. It is as if an increased rapidity of production of cells had taken the place of production of the usual secretion.

The distribution of the glandular dilatation in enlarged prostate is a matter of the utmost importance and significance. Under this heading, four observations are to be separated:

(1) Many enlarged prostates, on gross section, show here and there all over the cut surface small but still macroscopic, round, fleshy nodules or kernels looking like minute fibroids. Microscopically, these always have for their essential structure one system of enlarged acini. These are the "pseudo-adenomata" of Ciechanowski. Each consists apparently of all the elementary glands which originally arborated into a single duct; obstruction of this common duct by contraction of the new fibrous tissue about it has caused retention of the secretion of all the tributary acini, and their passive dilatation has resulted. In the dilatation, the muscular and elastic layers surrounding each gland of this individual system of glands have been stretched out, have lost their infoldings, and remain, finally, as a distinct spherical capsule round a mass of dilated glands.

Such "pseudo-adenomata" may be seen well distributed all through the two side-lobes, and may be the essential factor of their general enlargement. One lateral lobe alone may suffer enlargement of this type, and much less commonly a middle lobe may develop in this manner.

(2) Another principal, but never distinct, form of enlargement is where the obstructive dilatation of glands does not

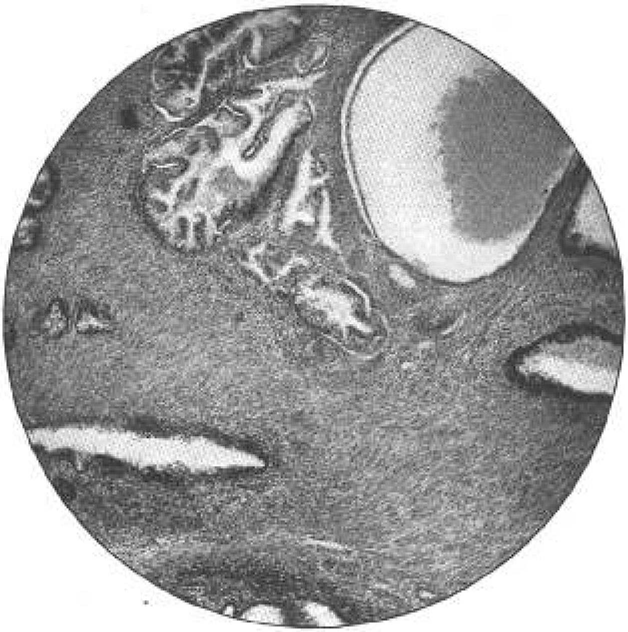

Fig. 13.—Showing the single row of flattened epithelium in a dilated gland; glands in various stages of dilatation; round-cell infiltration.

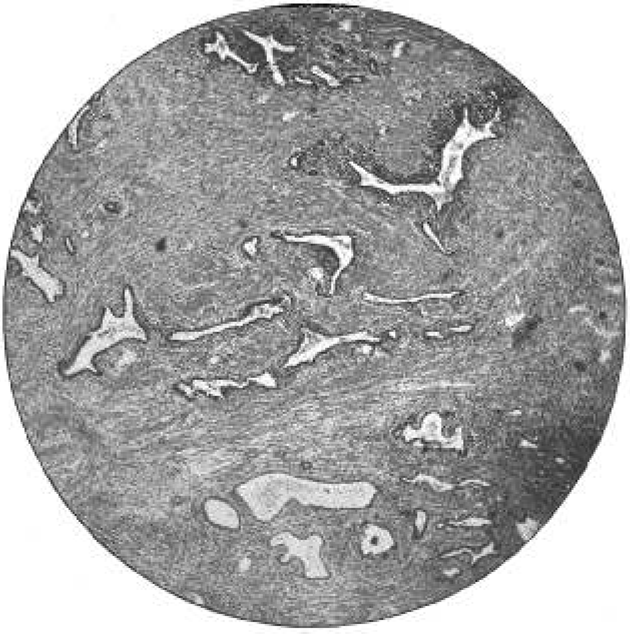

Fig. 14.—Showing glands dilated, with flattened epithelium; other glands and ducts compressed by fibrous tissue and showing subepithelial round-cell infiltration.

take place in isolated minute gland systems, but shows itself in glands here and there not drained by a common duct. The picture then shows, in one place, one or more relatively large cysts or abscesses; in another place, glands squeezed to partial or complete obliteration (Fig. 14); in another place, a perfectly normal area. In describing these two forms of microscopic change,—that resulting in the formation of knots or nodules, and that which is more diffuse and irregular, not obstructing definite gland systems,—it is quite apparent that the difference is not one in the kind of change, but in its distribution. There seems to be no pure form of enlargement. Every case presents a mixed form, and the different varieties may be seen in one section. It should be here observed that there seems to be no sound evidence that the obstruction to free drainage of prostatic acini lies anywhere but in the surrounding stroma. It has been suggested that the amylaceous bodies obstruct the ducts; but this cannot be true in most cases, because the presence of these bodies is inconstant within the dilated glands; and, furthermore, in half the glands, the bodies are seen in a proximal or peripheral position where they could not obstruct. Analogous examples of obstruction of exit-ducts by pressure of contracting stroma are seen in the formation of minute cysts in chronic mastitis and in varieties of chronic nephritis.

(3) For prostatic enlargement to involve the anterior commissure is exceedingly rare. As has already been suggested, this fact seems particularly significant. Ciechanowski[1, p. 266,] has collected only seven cases in all the literature where the anterior commissure was affected, and he quotes Aschoff,[6] who has shown that only a few or no gland tubules exist in this portion of the prostate. If, now, these glands or their muscular coats caused prostatic enlargement by neoplastic growth, there is no reason why such development, that is, a multiplication of glands, should not take place in the anterior commissure as well as in other parts; but inasmuch as passive dilatation of already existing glands is the cause of enlargement, these glands of the anterior bridge, the same in origin

and structure as all other prostatic glands, are merely too few in number and too small to be able to exhibit macroscopic changes. There are exceptions to this rule.

(4) For the last and most important observation on the fine distribution of the proliferative changes within the senile prostate, all credit for originality is, without question, due to Ciechanowski. In enlarged prostate, the new connective tissue, the contracted scar-tissue, and other signs of proliferation are seen most abundantly in the deepest portions of the gland, that is, midway between the periphery and the urethra, extending usually towards the urethra. There is, then, obstruction of exits, that is, of distal ducts, those nearest the urethra, and consequent retention of glandular secretion and other products of epithelial activity in the proximal or peripheral parts of the gland system. The obstruction is gradual, and at this period the muscular coat of each gland may hypertrophy to expel the glandular contents against opposition. Complete obstruction being established, passive glandular dilatation proceeds and general enlargement results.

When, now, atrophic prostates, that is, those below normal in weight, are studied [1, p. 282,] unexpected and ample confirmation of this simple hypothesis of an almost mechanical method of production of prostatic enlargement is found.

Abnormally small prostates seem to be of two varieties. The first includes those which accompany lack of development or loss of the testes. In this variety the tubules are narrow, are only elemental in branching, and the epithelium is small and not active. The second variety of small prostate is found in old men where the testes are normal, and on section such prostates appear in many respects similar to the enlarged ones. The small round cells, the new connective tissue, the scar-tissue, and the amylaceous bodies are all present. The glands, on the other hand, are small and compressed. The new contractile tissue has formed round the primary acini, in other words, more in the periphery of the prostate. The glands at their origins are compressed; their secretion, far from being retained, is expressed, and the whole prostate diminishes in size.

It seems warrantable, with regard to *conclusions on the histogenesis of enlarged prostate,* to add such weight as I may, as have Greene and Brooks[27] recently, by reaffirming the conclusions of Ciechanowski:

" The so-called enlargement of the prostate, as well as certain forms of prostatic atrophy, are related histogenetically, and have a common cause. The two processes do not differ qualitatively, but only in the distribution, intensity, and localization of otherwise analogous changes.

" The common starting-point of the enlargement and certain forms of atrophy is to be sought in the productive connective-tissue processes which occur in the stroma, and according to the stage of their development can show different stages of repair, but are always in isolated masses, and principally arise directly under gland epithelium.

" If the stroma changes are located in the central prostate near the principal exits, the lumina are closed, secretion collects, and peripheral dilatation results. This dilatation is the more rapid and reaches a higher degree the more numerous and the nearer to the exits of the principal tubules the obstruction occurs, and also the higher the degree of the simultaneous intraglandular pathological processes. These consist mostly of active proliferation, followed by desquamation called catarrhal, and may end in a purulent process by the accession of leucocytes.

" The enlargement of the prostate is almost exclusively due to dilatation of glands. The new formed connective tissue is relatively unimportant, and the active participation of muscle tissue in enlarged prostate in the way of true myoma (great majority of cases) is unproved and doubtful.

" If the stroma changes take place principally in the periphery and near the blind ends of the tubules, then there is atrophy of the tubules, shrinking of the connective tissue in the stroma, and atrophy of the entire prostate. This is quicker and more intense if there is no endoglandular pathological process.

"According to the balance of these two processes, the prostate may be of normal weight, increased or diminished.

"Atrophy and enlargement are histogenetically and probably etiologically similar."

PART III.

ON THE CAUSE OF ENLARGED PROSTATE.

Since the earliest times, the distressing symptoms of enlarged prostate have been observed and their cause sought. According to Bernays,[8] the earliest mention of the prostate as the cause of many of the senile bladder symptoms was in the writings of Morgagni, printed in 1761. His opinion was corroborated by John Hunter in 1786, in his "Treatise on the Venereal."

It seems necessary, in considering the etiology of enlarged prostate, to take the space here first to summarize briefly the beliefs of the best observers on this subject, because even now widely divergent opinions are still held.

One of the earliest opinions seems at the present time, as is not infrequently the case, to be one of the best. Desault,[15] a follower of John Hunter, in 1813, first suggested the inflammatory origin of enlargement of the prostate, saying that it was common in those who have had many attacks of gonorrhœa.

Home,[38] about the same time, proposed as the underlying cause the habitual congestion of the parts about the bladder-neck, such as might be brought about in high livers or in people who sit much.

Mercier,[54] in 1841, considered the cause to be sluggish circulation of the parts, such as one expects in men with much fat, or with sedentary habits. Such men, he says, have relaxed veins and most often suffer from prostatic enlargement.

Astley Cooper,[13] in 1824, declared the affection was the result of age alone and only physiological. In this view many have concurred, particularly French writers. Thus, Launois,[43] Regnauld,[67] and Guyon [32] have all contended in recent years

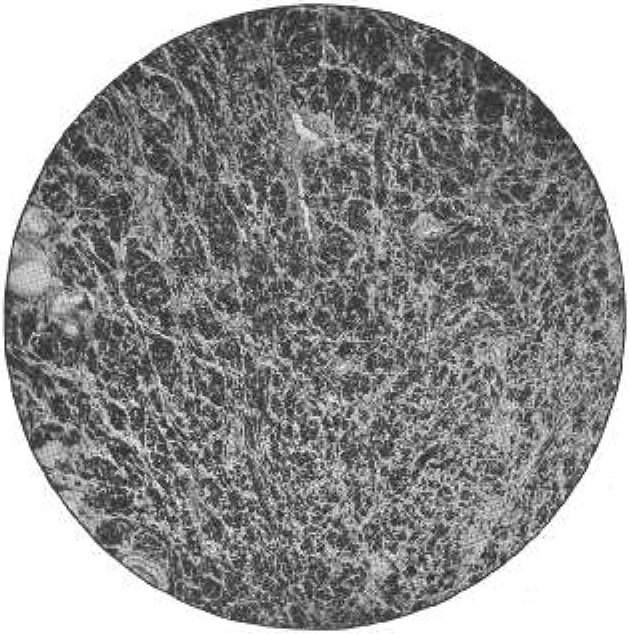

Fig. 15.—Showing infiltration of fibrous tissue between the smooth muscle-fibres of enlarged prostate.

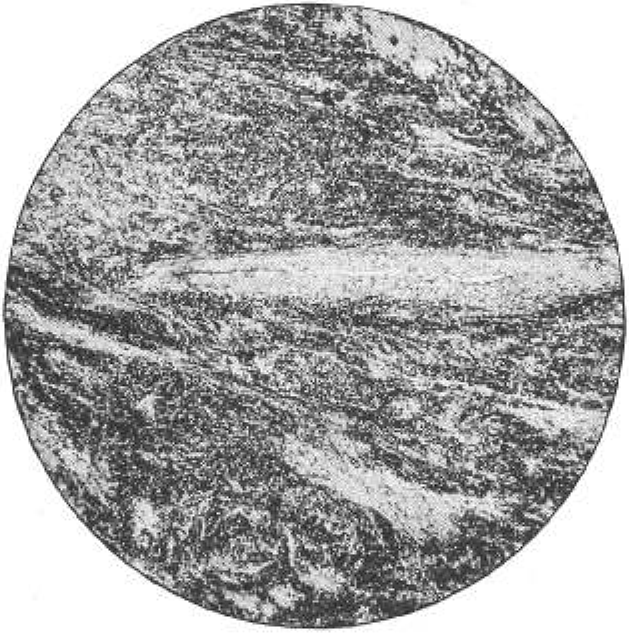

Fig. 16.—Showing diffuse, small round-cell infiltration and also arteriosclerosis in a small vessel.

that prostatic enlargement is a senile involution in the physiological sense.

Next, there are many[4, 7, 19, 21, 26, 28, 36, 39, 44, 45, 49, 57, 58, 62, 77, 78, 79] who base their theories of prostatic enlargement in one way or another on the apparent parallelism of development and function between the prostate and the testes. Lydston[46] combines congestion with sexual "prostatic overstrain" as a cause.

Syphilis, gout, rheumatism, stone, and stricture have been considered among etiological factors, but are spoken of now only to be at once excluded, since the beginning of modern pathological histology.

The bearing of arteriosclerosis, local and general, and of bladder-wall changes, we have already considered at great length, and have decided that, as a constant etiological factor in the production of actual increase in the size of the prostate, it may be ruled out. It is seen in the enlarged prostate (Fig. 16) and in that of normal size.

Finally, there is the belief that the enlarged prostate is suffering from a true new growth,—single or multiple fibroma or fibromyoma. Of the adherents of this theory, the most prominent is Thompson, who says[72, p. 131,] "Inflammation must be eliminated from the category of alleged causes," arguing that chronic inflammation would cause eventual shrinkage rather than increase in size. He draws an analogy, already referred to, between the uterus and the prostate as to their origin, and states that, just as at the close of functional activity, the uterus is liable to develop new growths similar in structure to its own, so in the prostate, at a similar stage of development in the male, a similar proneness to growths like itself in structure may be seen. Recent writers who still believe in the fibromyomatous prostate are few.[35] Maguire probably best summarizes their view when he says,[46] "Sometimes the obstruction is due wholly, or in part, to fibroma, single or multiple, of the prostate. They form distinct encapsulated growths. These tumors are like the fibromyomata of the uterus; of their etiology, I can offer you no conjecture."

As a last word in this list of hypotheses, it should be said that no one, so far as I can discover, still considers enlarged prostate to be a true hypertrophy.

It only remains, now, to discuss briefly in the light of modern pathology some of the more important theories in the list above.

1. The Relation of the Testes to Enlarged Prostate.—The theory of the dependence of enlarged prostate with its sequelæ on the testes is based upon (*a*) the parallel physiological development of the two; (*b*) on the arrest of development of the prostate after an arrest of testicular growth; (*c*) on atrophy of normal prostate after castration in animals and youths.

The observations on which this theory is founded are correct. There is undoubtedly in animals a near relation between castration or resection of the vas deferens and atrophy of the normal prostate. The histology of such prostate shows, as has been noted, a true atrophy of all elements. The supporters of the belief that prostatic enlargement, on the one hand, is due to a senile diminution of testicular function, and at the same time, on the other hand, advocate castration as a therapeutic measure to retard the enlargement, contradict their own observation. For[1, p. 288,] as a proof of the correlation between the fact that castration causes prostatic atrophy as a result of the development of the prostate and the testes, they bring forth loss of sexual function; while in the same argument they declare that prostatic enlargement is due to some senile loss due to diminished testicular activity. In short, they contend that the original prostatic enlargement or the later diminution after castration are both due to loss of sexual function. This position is not tenable. Moses[59] reports enlargement of the prostate in a man of sixty-eight some years after a double complete castration, thus proving beyond doubt that the changes seen in enlarged prostate undoubtedly develop independently of the presence or absence of the testes.

White,[77, 78] Moullin,[57] and Harrison[36] have been the most ardent champions of a therapeutic application of this theory;

though I believe I am correct in saying that White no longer believes such an application to be uniformly indicated.[79] White's belief was based on experiments upon dogs, and since his first reports several [12, 45, 67] have worked on similar lines. It appears to be now established that in all animals except dogs castration is always followed by prostatic atrophy. In dogs, the results are variable; one case, for example,[45] five months after double vasectomy, showed a very large prostate. It is to be noted at this point that the dog, which is the only animal where prostatic atrophy does not always follow castration, is, according to the veterinarians [1, p. 290,] the only animal that suffers from prostatic inflammation.

Cabot,[10, 11] too, entirely from the clinical point of view, has ably controverted the hypothesis of a connection between the testes and enlarged prostate. It is true that the prostate in the living, nothing being known of its histology, has without question, after castration, diminished in size. But it is also true that enlarged prostate is much more often seen in the living than it is found on the autopsy table. There is, in short, evidence that pressure, irritation, and inflammation at the bladder-neck produce their usual sequelæ of congestion, œdema, and even evanescent hyperplasia, and that these conditions may all be relieved and made less by the diminution of blood supply and by the functional inactivity which must follow castration. Indeed, the diminution in size follows too quickly to be a true tissue atrophy. Take, for example, a case operated by Gavin,[25] where the patient a few hours after castration passed urine voluntarily for the first time in months. Cabot says, " There are numerous cases in my practice in which removal of a stone had been followed by such subsidence of irritation at the vesical neck that no operation on the prostate was necessary;" and he, too, concludes that " no more wholly unsupported theory has been advanced in the whole discussion than that quick relief which sometimes follows castration is due to a rapid process of atrophy."

Englisch, in Vienna, is now making a physiological clinical study of the relation between the prostate and testes, and Ciechanowski is also working on this problem.

2. Is Enlargement of the Prostate Neoplastic in Origin?—Beginning with Velpeau [73] and Thompson, those who believe the enlarged prostate to be a true new growth, usually fibromyomatous in character, are many, either by declaration or implication.

The facts that the prostate is purely a genital organ, as has been definitely established,[75] and that it contains the uterus masculinus, give ground for the reasoning that fibromyomata may arise in the prostate analogous to those found in the uterus.[35] Grossly, however, the largest prostate is only occasionally as large as the average uterine fibroid. Fibromyoma of the uterus, even the intramural form, may in most cases be sharply differentiated by the eye, at least, as a definite tumor. The prostatic tumor, if a fibroid, must be considered atypically diffuse. Microscopically, the myomatous part of the uterine fibroid is more cellular, and the nuclei are usually more uniformly distributed than in the prostatic tumor, that is, there are fewer of the hyaline fibrous areas resembling scar; and in the prostatic growth also, in practically every field, may be found the remains of at least one or more glands. Such glands, of course, are rarely seen in uterine fibromyomata.

In those prostatic tumors which most resemble fibromyomata (Fig. 15), careful study shows that the distribution of muscle-bundles is brought about, not by a new growth of them, but rather by subdivision and separation of old bundles due to the ingrowth and expansion of new connective tissue. It has been already shown, also, that the "knotty" form, where small round bodies resembling small fibroids shell out, is always glandular in its origin. Jones [39, p. 240,] has never seen pure myoma of the prostate; Virchow [74] says it is very rare, and with this Motz [55, p. 254,] agrees.

A recent study [3] of 100 prostates from men dead of prostatism showed fourteen cases said to be adenocarcinoma. This seems an undue proportion of true malignancy, and, so far as present figures go, can hardly be taken as an usual percentage.

It is to be concluded, therefore, that true fibromyoma as well as true adenoma may occur, but that neither is the condition found in the usual benign senile enlargement of the prostate.

3. Is Enlargement of the Prostate a Senile Involution?—The affirmative reply to this inquiry is not to be lightly cast aside. We have seen that there may exist a purely senile atrophy of bladder-wall muscle with a new growth of connective tissue infiltrating the muscles. Such a new growth of connective tissue may take place as part of a purely degenerative process, as is apparently seen in chronic mastitis and in chronic interstitial nephritis. Such connective-tissue formation following degeneration is accompanied by the presence of small, round mononuclear cells, and such tissue has also its characteristic power to contract and cause constriction. It is impossible therefore, at present, to exclude senile degeneration as one, at least, of the causes of enlarged prostate.

4. Is Enlargement of the Prostate Inflammatory in Origin?—The best work on this question has been done by Finger [22] and Ciechanowski,[1, 2] and from them I shall transcribe freely.

It has been the custom clinically to separate chronic prostatitis from senile enlargement; the principal ground for this being (*a*) that many individuals suffering from prostatism forget, truly or not, that they have had in the past an inflammatory affection of the urethra or prostate; (*b*) chronic prostatitis may be frequently differentiated in diagnosis from the commoner senile enlargement. This, however, as has been pointed out [1, p. 291,] may well be only an example of the remote connection which may exist between the cause and the ultimate appearance of a disease. That is, this latent relation between infection and senile enlargement may be similar to the apparently undoubted connection between syphilis and the later central nervous affections, or the relation between rheumatism and the chronic valvular cardiac disease discovered many years later; (*c*) the objection of Thompson that inflammatory disease should cause shrinking rather than enlargement has already been met by showing that the essential change is a shrinking, but that the shrinking may be about exit-ducts and be followed by proximal gland dilatation. It may be, in fact, compared to the constriction of the pylorus which is followed by dilatation of the stomach. Furthermore, infectious processes may be the basis of increase in volume of tissue, as witness thickenings of the pleura, infectious granulomata, the development of tuberculous tissue, and others. Finger (loc. cit.) concludes that the changes of chronic prostatitis are identical with those of senile enlargement. In both there is a catarrhal gland inflammation, a subepithelial, periglandular, round-cell infiltration, and in both the process is in clumps and irregular in distribution. The importance of such differences in intensity and distribution of the inflammation, that is, quantitative differences between prostatitis and enlargement, lies in the fact that they explain differences in clinical symptoms between the two. The amount and intensity of inflammation particularly explain the late and slow onset of enlarged prostate, it being fair to conclude that the latter is always the result of an infection long latent and of such slow onset that the infection may indeed be forgotten. In both processes, described clinically as chronic prostatitis and enlarged prostate, the beginnings seem always to be in and about the glands and ducts and not near vessels; in other words, they are both ultimately of urethral and not of hæmatogenous origin.

The underlying inflammation is, of course, gonorrhœa. That an attack of this infection should not be remembered is, as a matter of fact, unnecessary. Patients in whom strictures are found[1 p. 296,] will declare they never had gonorrhœa or instrumentation. Many observers[30, 60, 63] quoted by[1] have proved that gonorrhœa may be primary in the prostate, and others[20, 23, 31] have shown that the disease may remain in the posterior urethra for a long time latent and quite unsuspected. Posterior urethritis is said by some[9] to occur in 93 per cent. of cases with anterior urethritis, and in many of these cases there is a definite prostatitis.

The direct proof of finding gonococci in the sections of enlarged prostate remains unmade. Councilman[14] first demonstrated their presence in the prostate, and others[60] have shown them to be present in prostatic milkings. These instances, however, were in fairly acute inflammations; and, if it were difficult here, it is little wonder that they may not have been found in such a chronic and such a mild process as the senile enlargement.

Ciechanowski collects certain indirect facts which tend to confirm belief in the corelation of gonorrhœa and the enlarged prostate.

(1) The frequency of gonorrhœa;

(2) The frequency of chronic gonorrhœa in the posterior urethra and prostate, *i.e.*, in 1070 cases[70] the process was in the deep urethra in 424;

(3) The frequency of cystitis; and, lastly,

(4) The only domestic animal that suffers from enlarged prostate is the dog; and the male dog, too, seems to be the only animal that has a true purulent urethritis which is infectious.[41]

Kryzysztalowicz[1, p. 299] collected 121 strictures in ninety-nine persons, of whom sixty had suffered from long-standing gonorrhœa, and five still had it; ages between forty and sixty years. Most of them first showed demonstrable signs after fifty years of age. This proves that often many years may elapse after the chronic gonorrhœa before stricture appears; that gonorrhœal infection, in other words, may be latent and forgotten for many years and yet be potent.

And, finally, as Ciechanowski[1, p. 300] has made perfectly clear, a characteristic of the advance of a gonorrhœal process is that it is not by continuity but by jumps, and the distribution of diseased foci separately here and there over the prostate is distinctly a feature in senile enlargement.

From this review, therefore, I make the following Conclusions on the Cause of Enlarged Prostate:

(1) The underlying cause of the usual form of prostatic enlargement and of certain forms of prostatic atrophy is a slow formation of new connective tissue due to infection or to infection aggravating a senile degenerative process.

(2) The gonococcus is probably most often the specific infection because (*a*) of its great frequency; (*b*) other inflammatory causes are not common in the parts in question; (*c*) a great similarity exists between the histology of gonorrhœal processes and those seen in these senile prostates.

(3) Neoplasms, fibromyomata, and adenoma occur, but may be called rare.

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